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Please file the following enclosed patent application papers:

Applicant #1, Name: Eric H. Kuhrts
Other Applicant(s): ~~Other Inventor Names~~
Title: "Sustained-Release Microencapsulated Delivery System" Title

- (Xx) Specification, Claims, and Abstract: Nr. of Sheets 21 Number of Pages
(X x) Declaration: Date Signed: 2000 February 1 Date Signed
(x) Drawing(s): Number of Sheets Enclosed: (In Triplicate):
Formal: Number of Formal Drawings
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(Xx) Small Entity Declaration of Inventor(s)
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Inventor:

Eugene Kuchars

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In the United States Patent and Trademark Office

First/Sole Applicant: Eric H. Kuhrts
Other Applicant(s): None Other Inventor Names
Title: "Sustained-Release Microencapsulated Delivery System" Title

Small Entity Declaration - Independent Inventor(s)

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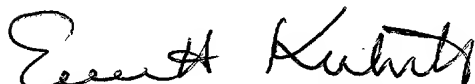
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SUSTAINED-RELEASE MICROENCAPSULATED DELIVERY SYSTEM

Inventor: Eric H. Kuhrts

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a process for manufacturing pharmaceutical formulations that results in sustained-release microparticles. These microparticles release a therapeutic agent gradually in a consistent fashion over a prolonged period of time, and can be manufactured in a way to yield a high percentage of drug core at a very economical cost. The process consists of heating and mixing a vegetable oil with a very high melting point with a therapeutic agent or drug until well coated, and then cooling to room temperature until hard. The resultant particles are small, free flowing, and exhibit release profiles that can be adjusted to extend from 6-24 hours. Other fibers, sugars, or polymers can be added in layers as an outer coat after cooling to effect the release profile and the hydrophobic properties of the particles, or directly to the matrix to accelerate drug release by creating additional channels for diffusion during erosion while dissolving. Other substances such as minerals can be added to the cores to provide additional weight to the particles causing them to sink due to heaviness.

The benefits of producing sustained-release formulations of drugs or other therapeutic agents is now widely recognized in the medical literature and is utilized in many commercial products. It is important to distinguish at the out-set between solid monolithic dosage forms such as tablets, and powders, and particles that are loosely packed into capsules. A sustained-release powder consists of microparticles that are microencapsulated using a manufacturing process that enables them to be ingested, as, for example a powdered drink-mix which can be added to a liquid and still retain its sustained-release and taste masking properties, or encapsulated in two piece hard shell gelatin capsules. Microencapsulated powders may behave differently when subjected to the high pressures required to form tablets, and may fracture in the process. In addition, sustained-release tablet formulations may employ other techniques that emanate from their large size,

surface area and the swelling properties of hydrocolloids. In this case, diffusion and solubility issues become important for sustained-release.

In the present invention, the drug particles are processed in a way to yield a high percentage of active component powder that is still small enough to be virtually indistinguishable from the original drug particles themselves. Surprisingly, drug cores consisting of 95% of the active agent are possible that release over a full 24-hour period.

In general, sustained-release dosage forms are multi-particle formulations that when ingested in capsule form, rapidly disintegrate into a large number of subunits. This is fine for drugs that are effective at relatively low doses, or dose levels that can fit into a capsule that is a reasonable size. The amount of drug that can fit into a two piece hard shell capsule that is easy for most people to swallow is at most about 800 mg. based on bulk density of the compound. But when large doses are required, such as for example with nutraceuticals, amino acids, or botanical substances, it is desirable to take them in a powder dosage form that can be mixed with a liquid and consumed.

There are many different ways to microencapsulate drugs producing sustained-release. Many of these methods can be found in "Microcapsules and Microencapsulation Techniques", 1976, M.H. Goucho, and Microcapsules and other Capsules, 1979, also by M.H. Goucho. Another resource book is "Aqueous Polymeric Coatings For Pharmaceutical Dosage Forms", 1989, Marcel Dekker, Inc. Most of the methods of producing sustained-release microparticles can be classified into either physical or chemical systems. Physical methods would include such techniques as pan coating, gravity-flow, centrifuge, and the Wurster Process. The Wurster Process employs a high velocity air stream that is directed through a cylindrical fluid bed in which the particles are suspended in the air. A coating is sprayed onto the suspended particles, and the particles flow out the top of the cylinder and descend back to the layer of fluid. The flow of air-dries the coating, so that successive layers can be applied repeatedly by further spraying. Variables that control the process include the number of cycles, temperature, pressure, and humidity, and can be used to provide the desired coating composition and thickness.

Chemical methods of microencapsulation are usually coacervation or phase separation. This technique involves dissolving the membrane forming polymer in a suitable solvent or vehicle and the drug to be dissolved is suspended in this solution and kept under agitation. The coating precipitates onto a droplet of the drug, similar to crystallization.

Fluid bed granulation or coating is one of the most common techniques used at the present time for small particle sustained-release. Fluidized bed equipment is available as “top spray”, bottom spray”, and “tangential-spray”. The core drug is first preheated in the vessel to about 30°C with hot air, placing the particles in suspension. The floating particles are then sprayed with an aqueous suspension to provide a coating, while drying at the same time. Inlet temperature, spray rate, and air throughput must be adjusted to provide optimum end product. Furthermore, the finished particles must be subjected to a post-drying period at around 40°C, where any residual moisture can be driven off. In some case, this last drying period may be up to 24 hours.

Many of the polymers that are used to provide sustained-release properties to powders in the fluid bed process require solvents such as acetone, isopropyl alcohol, chlorinated solvents, alkanes, methyl ethyl ketone, cyclohexane, toluene, carbon tetrachloride, chloroform, and the like. Evaporation of the solvents becomes an environmental concern, and in many states, it is illegal to release these emissions into the atmosphere. Aqueous or water based polymers are limited mainly to ethyl cellulose and methacrylic acid esters such as poly methacrylate dispersions. In addition, 10-20% of a suitable plasticizer such as triethyl citrate must be added to the polymer. For example, U. S. patent # 5603957 uses a solvent-based polymer system to deliver aspirin over a 24-hour period. Preferred solvents are acetone/alkanol mixtures, or cyclohexane, toluene, or carbon tetrachloride. Castor oil, a low melting point oil, is also included in the polymer solvent mix.

Typical aqueous ethyl cellulose polymers currently in wide use include; Surelease®, Colorcon, West Point, PA, and Aquacoat®, FMC Corporation, Philadelphia, PA. In the Aquacoat® brochure available on their web site, it is recommended that for sustained-release applications, at least a two hour curing time at 60°C be conducted to insure reproducible release profiles. This should be done in a tray dryer. Subjecting drugs and other therapeutic compounds such as

botanical extracts to 60°C temperatures for 2 hours or more is likely to result in a loss of potency or degradation of active principles, and is especially problematic for substances with low melting points. Botanical extracts, in particular, have many volatile compounds that can be destroyed if kept at high temperatures for long periods.

Another polymer in common use for sustained-release applications is Eudragit®, Huls America, Somerset NJ. This is a neutral methacrylic acid ester with a small proportion of trimethylammonioethyl methacrylate chloride. This polymer is also applied using the fluid bed process, or can be used in a standard wet granulation procedure. Wet granulation involves mixing the drug or therapeutic agent with water in a conventional high-speed mixer until a pasty mass, and then dried in an oven over 24 hours at 60°C.

Carnauba wax has also been used to produce sustained-release dosage forms. Usually, at least a 15% level of wax is applied to the drug for the core, followed by a further coat of ethyl cellulose and polyvinylpyrrolidone (PVP) at about 10 to 15% by weight. This results in drug levels in the cores that range from 50 to 70 %, with the other 50 to 30% being the wax and polymers.

Another method of producing sustained-release particles is by starting with sugar spheres or nonpareils. The sugar spheres are also processed in a fluid bed granulator, but the drug must be dissolved in an aqueous solution and sprayed onto the sugar spheres, followed by spray coating with polymers that produce sustained-release as previously mentioned. This system results in large particles that are not acceptable in most drink mix applications, and botanical extracts cannot be dissolved enough to use in this system. The therapeutic agent needs to be absorbed

into the sugar particle. The smallest starting particle size for non-pareils is about 60 mesh (US standard sieve number). After coating, the particles are often 30 mesh and larger. The large particle size also presents a problem when encapsulating or tableting.

Melt-spinning techniques involve subjecting a therapeutic agent to sustained heat treatment with a melted polymer which is pumped at a constant rate under high pressure through a plate having a number of small holes, referred to as a spinneret. Filaments emerge from the spinneret into air where they are cooled. These filaments are made into sustained-release formulations. In this process, a polymer is melted on a hot grid or by extrusion-type screw, and then passed to a metered pump. U.S. Patent Nos 5445769 and 5458823 describe the use of a type of melt-spinning technique called a liquiflash spheronization or liquiflash microspheres. Temperatures as high as 130-240 degrees C are often required in this process. In addition, the polymers for the final coats are dissolved in solvents such as acetone and sprayed onto the microspheres in a fluidized bed apparatus with a Wurster column.

U.S. Patent No. 5700471 involves subjecting an aqueous dispersion of a drug or dye to turbulent mixing at a temperature that is above the melting point of the dye or drug, producing a melt emulsion which is then spray dried or converted into a suspension by cooling.

A hot melt technique is described in U.S. Patent No.5718921 in which a polymer is dissolved in a volatile organic solvent, and the drug is dispersed or dissolved in the polymer solution. The mixture is then suspended in an organic oil, and the organic solvent is extracted into the oil, creating microspheres. In this process, silicon oil, vegetable oil, paraffin, and mineral oil are used. These are all low melting point oils.

U.S. Patent No. 4855326 discloses combining sugar with low melting point oils such as vegetable oil, baby oil, margarine, cocoa butter and the like to help overcome hydrophobic properties and facilitate dispersion in water. None of the oils are solid at room temperatures or have high melting points. The oils themselves are not providing sustained-release properties.

In another process, ethyl cellulose, polyvidone and a small amount of castor oil are dissolved in acetone and isopropanol and sprayed onto aspirin particles in a fluid bed granulator such as is described in U.S. Patent No. 5603957. In this case the oil is liquid at room temperatures, and is being used as a plasticizer. The polymers are providing the sustained-release properties, not the oil. Castor oil itself cannot be used as a solid coating material because of its low melting point.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide a sustained-release microencapsulation process that can be produced inexpensively and quickly and result in a very high percentage of active substance in the core. It is a further advantage of the instant invention not to necessitate the use of solvents or synthetic polymers, although polymers can be used as an additional means of control if desired. It is a further advantage of the present invention not to require extremely high temperatures to produce the microspheres, and to shorten the length of time the materials are processed or exposed to elevated temperatures.

In accordance with the invention, there is provided a microsphere that is produced by mixing the therapeutic agent with a hot vegetable oil with a melting point at least above 110°C, and preferably about 160 degrees F, in a vertical or horizontal high intensity shear mixer until the particles of the core substance are thoroughly mixed with the oil, and then cooling the hot melt to produce fine particles that exhibit excellent sustained-release properties. Surprisingly, the entire process can be completed in about 10 minutes or less, utilizing the work input of the mixer to melt the oil and intimately mix it with the core agent. The ideal high temperature melting point oil for this process is a hydrogenated soy oil with a maximum iodine value of 5.0 and a melting point of 150-160°C. Such an oil with these specifications is Dritex S® in flake form or Sterotex HM® which is a spray chilled, powder. Both are available from AC Humko, Memphis TN. The melting point profile is more uniform if the spray chilled powder is used.

purposes, but not as sustained-release agents. For example, soft oils are often used for suppositories. These oils cannot be used to provide solid particles at room temperature. Various resins and shellac have also been used, but usually not for sustained-release. Carnauba wax is widely used in pharmaceutical dosage forms.

An oil such as a hydrogenated soy oil with an iodine value of at about 5, and a melting point above 120 degrees F, will be solid at room temperatures. In fact, such an oil or fat with a melting point above 145 degrees F will allow melting to occur only at temperatures that are significantly above those temperatures normally encountered by food or pharmaceutical products, even during shipment on hot days. Just such an oil is Sterotex HM®, manufactured by AC Humko, Memphis TN, a spray chilled hydrogenated soy oil that completely melts at about 160°F. This oil is completely solid at lower temperatures, and is available as a powder. Other oils of similar melting points are available, but are usually in a solid mass, and must be chiseled or chipped apart, and therefore are difficult to use and weigh out. Some oils are available in flake form such as Dritex S from the same company. Either product is preferable to the solid mass hydrogenated soy oils. Any oil with a melting point above about 110°F will work, but the most desirable would be those oils with melting points from 120-200°F, and ideally about 120-180°F. These melting points are usually below the melting point of most drugs or therapeutic compounds, and are achievable using the above described equipment.

Natural oils such as soy oil or other vegetable oils are most preferred. These oils are very acceptable to health conscious consumers, and appear user friendly on the label. Stearic acid is an oil that is derived from either animal or vegetable sources and has a melting point of about 70°C . USP stearic acid is primarily a mixture of stearic and palmitic acids.

The core material may be selected from any suitable drug, therapeutic or prophylactic agent, food or botanical substance, fertilizer, or animal feed, which can be incorporated in the hot melt without losing substantial activity for the chosen therapy. A broad range of materials are therefore useful. Representative non-limiting classes of drugs useful include those falling into the following therapeutic categories:

Ace-inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatics; anti-cholesterolemics; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti-histamines; anti-hypertensive drugs; anti-infectives; anti-inflammatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor drugs; anti-tussives; anti-uricemic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; angiogenesis inhibitors; antacids; antiarthritics; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; botanical substances, bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystokinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastro-intestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics; hypoglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; NSAIDS; nutritional additives; peripheral vaso-dilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vaso- constrictors; vago-dilators; vertigo agents; vitamins; wound healing agents.

Non-limiting examples of specific therapeutic agents which may be useful in the present invention can be chosen from the list which follows. Mixtures of these agents and their salts used for appropriate therapies are also contemplated: acetaminophen; acetic acid-, acetylsalicylic acid and its buffered form; albuterol and its sulfate; alcohol; alkaline phosphatase; allantoin; aloe; aluminum acetate, carbonate, chlorohydrate, hydroxide- alproazolam; amino acids; aminobenzoic acid; amoxicillin; ampicillin; ansacrine; amsalog; anethole; ascorbic acid; aspartame; aspirin, atenolol; bacitracin; balsam peru; BCNU (carmustine) beclomethasone dipropionate; benzocaine; benzoic acid; benzophenones, benzoyl peroxide; bethanechol; biotin; bisacodyl; bomyl acetate; brompheniramine maleate; buspirone; caffeine; calamine; calcium, calcium carbonate, casinate and hydroxide; camphor; captopril; cascara sagrada; castor oil; cefaclor; cefadroxil; cephalixin;

cetylalcohol; cetylpyridinium chloride; chelated minerals; chloramphenicol; chlorcyclizine hydrochloride; chlorhexidine gluconate; chloroxylenol; chloropentostatin; chlorpheniramine maleate; cholestyramine resin; choline bitartrate; chondrogenic stimulating protein; cirnetidine hydrochloride; cinnamedrine hydrochloride; citalopram; citric acid; cocoa butter; cod liver oil; codeine and codeine phosphate; clonidine and its hydrochloride salt, clorfibrate; cortisone acetate; ciprofloxacin HC I; cyanocobalamin; cyclizine hydrochloride; danthron; dexbrompheniramine maleate; dextromethorphan hydrobromide; diazepam; dibucaine; diclofenac sodium; digoxin; diltiazem; dimethicone; dioxybenzone; diphenhydramine citrate; diphenhydramine hydrochloride; docusate calcium, potassium and sodium; doxycycline hyclate; doxylamine succinate; efavirenz; enalapril; enoxacin; erythromycin; estropipate; ethinyl estradiol; ephedrine; epinephrine bitartrate; erythropoietin; eucalyptol; ferrous fumarate, gluconate and sulfate; folic acid; fosphenytoin; 5-fluorouracil (5-FU) fluoxetine HCl; furosemide; gabapentin; gentamicin.- gemfibrozil; glipizide; glycerin; glyceryl stearate; griseofulvin; growth hormone; guaifenesin; hexylresorcinol; hydrochlorothiazide; hydrocodone bitartrate; hydrocortisone and its acetate; 8- hydroxyquinoline sulfate; ibuprofen; indomethacin; inositol; insulin; iodine; ipecac-, iron; isoxicam; ketamine; koalin; lactic acid; lanolin; lecithin; leuprolide acetate; lidocaine and its hydrochloride salt; lisinopril; liotrix; lovastatin; luteinizing hormone; LHRH (luteinizing hormone releasing hormone),- magnesium carbonate, hydroxide, salicylate, trisilicate; mefenamic acid; meclofenamic acid; meclofenamate sodium; medroxyprogesterone acetate; methenamine mandelate; menthol; meperidine hydrochloride; metaproterenol sulfate; methyl nicotinate; methyl. salicylate; methylcellulose; methsuximide; metronidazole and its hydrochloride; metoprolol tartrate; miconazole nitrate; mineral oil; minoxidil; morphine; naproxen and its sodium salt; nifedipine; neomycin sulfate; niacin; niacinamide; nicotine; nicotinamide; nitroglycerin; nonoxonyl-9; norethindone and its acetate; nystatin; octoxonyl; octoxonyl 9; octyl dimethyl PABA, octyl. methoxycinnamate; omega-3 polyunsaturated fatty acids; orphenazone; oxolinic acid; oxybenzone; oxtriphylline; para-aminobenzoic acid (PABA); padimate O; paramethadione; pentastatin; peppermint oil; pentaerythritol tetranitrate; pentobarbital sodium; pheniramine maleate; phenobarbital; phenol; phenolphthalein; phenylephrine hydrochloride; phenylpropanolamine and its hydrochloride salt; phenytoin; phenelzine sulfate; pirofenol; piroxicam; polymyxin B sulfate; potassium chloride and nitrate; prazepam; procainamide hydrochloride; procaterol; propoxyphene and its HC I salt;

propoxyphene napsylate; pramiracetin; pramoxine and its hydrochloride salt; propranolol HC I; pseudoephedrine hydrochloride and sulfate; pyridoxine; quinapril; quinidine gluconate and sulfate; quinestrol; ralitoline; ranitadine; resorcinol; riboflavin; salicylic acid; sesame oil; shark liver oil; simethicone; sodium bicarbonate, citrate and fluoride; sodium monofluorophosphate; sucralfate; sulfanethoxazole; sulfasalazine; sulfur; tacrine and its FIC I salt; theophylline; terfenidine; thioperidone; trimethrexate; triazolam; timolol maleate; tretinoin; tetracycline hydrochloride; tolmetin; tolnaftate; triclosan; triprolidine hydrochloride; undecylenic acid; vancomycin; verapamil HC I; vidaribine phosphate; vitamins A, B, C, D, B I, B2, B 6, B12, E, K; witch hazel; xylometazoline hydrochloride; zinc; zinc sulfate; zinc undecylenate.

Useful dosage forms include without limitation oral forms such as tablets, capsules, beads, granules, aggregates, powders, gels, solids, semi-solids, and suspensions. Injectable forms, lotions, transdermal delivery systems including dermal patches, implantable forms or devices, aerosols or nasal mists, suppositories, salves and ointments are also useful.

In certain preferred embodiments, an amino acid like substance such as L-arginine, or L-carnitine, sports supplements such as creatine monohydrate, a vitamin such as niacin or vitamin C may be the core material. A therapeutic substance such as garlic powder, astaxanthin, or polygonum cuspidatum root extract would be examples of botanical substances. Also in this category would be tocotrienols or co-enzyme Q-10. An anti-histamine such as loratadine would be desirable in a 24 hour release profile. Blood pressure medication is also a preferred class of drugs. Fertilizers and fungicides would be non-drug applications for the process. Slow release of fertilizers and fungicides in the soil is especially desirable for nitrogen containing formulas. In a sustained-release microcapsule, the nitrogen fertilizer will tend not to leach out of the soil when wet.

A variety of additives can be incorporated into the inventive compositions for their intended functions. These additives are usually used in small amounts. In some cases, additives such as hydrocolloids are used as suspending agents, as for example in a powdered drink mix that is reconstituted in liquid.

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, rape seed proteins, blood proteins, egg proteins, acrylated proteins; water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, gum arabic, and related gums (gum ghatti, gum karaya, gum tragacanth), pectin; water-soluble derivatives of cellulose: alkylcelluloses, hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as: cellulose acetate phthalate (CAP), carboxyalkyl celluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethyl cellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVP/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water-soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Processing aids such as sucrose, polydextrose, maltodextrin, lactose, maltose, and the like may also be used. In some cases where accelerated release is desired, a sugar may be incorporated into the hot melt. Since the oil coating is hydrophobic, incorporating a hydrophilic sugar in the hot melt helps counteract the tendency of the particles to float. The sugar also helps to increase the rate of release of the core material by providing solubility to the matrix. Other substances such as calcium carbonate or other minerals can be added to provide weight to the particles and effect the release profile.

Examples of classes of additives include excipients, lubricants, hydrocolloid suspending agents, buffering agents, disintegrating agents, stabilizers, foaming agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, etc.

Examples:

Example 1:

Niacin (nicotinic acid) is added to a plow mixer, which was capable of operating at high temperatures because it was jacketed with a second layer to allow hot water to flow around the vessel. The unit was fitted with a tower-mounted, hydraulic atomizing nozzle with heated tanks and heated/insulated lines to enable hot oil to be applied at high temperatures. A high speed chopper operating at 10 hp was fitted at the discharge point. Hydrogenated soy oil flakes(Dritex S®, AC Humko, Memphis, TN) with a melting point of about 80°C or 140-160°F was sprayed on the powder as it was mixing in vessel. Efficient coating or microencapsulation of the powder was achieved in about 30 minutes when a temperature of about 155°F was reached and the hot oil thoroughly mixed with the powder. Cooling was achieved by discharging the batch into a cooler mounted directly below the mixer. The resulting granules were small, free flowing, and exhibited sustained-release properties when a dissolution test was conducted. The weight percent of the niacin in the finished product was 90%, and the hydrogenated soy oil was 10%.

Dissolution Test

Protocol: Basket method

Media: water

Paddle speed: 50 RPM

Time points/ % released: 1hr-28%, 2hr-38%, 3hr-44%, and 6 hours-45%

Example 2

The amino acid L-arginine free base, was charged to a Littleford W-10 high shear mixer with a hot water jacket to allow circulating hot water to keep the vessel hot . After mixing for 1 minute at 1000 RPM, spray chilled hydrogenated soy oil powder(Sterotex HM®, AC Humko, Memphis

TN) was added to the vessel. The work input was increased to 2000 RPM and then adjusted down to about 600 RPM for 5 minutes. The high shear of the mixer melted the oil and mixed with the core ingredients. Surprisingly, the work input of the mixer itself provided enough energy to melt the oil without the need of a heating tank and lines to spray the hot oil as in the previous example. The powder was discharged into a cooler mounted below the unit. The resulting particles were small, powder like, free flowing, and exhibited excellent sustained-release properties with a 24 hour release profile at only a 5% by weight of oil.

Dissolution test

95% L-arginine free base/5% hydrogenated soy oil

L-arginine base assay	100%	
Time Release Pattern	1 hour	20%
	2 hrs	23%
	4 hrs	30%
	6 hrs	35%
	8 hrs	40%
	16 hrs	70%
	24 hrs	100%

Example 3

Creatine monohydrate is charged to a Littleford high shear mixer with calcium carbonate (5% by weight) and sucrose (10% by weight) and mixed at 1000 RPM. Sterotex HM® hydrogenated soy oil is added at a 5% level and the speed of rotation is increased to 2000 RPM to melt the oil, and then decreased to maintain the power draw to within the allowable motor amperage.

Unexpectedly, after 3-5 minutes the oil is fully melted and mixed with the core materials, and upon inspection, the batch is fully granulated. The powder is discharged into the cooling unit and appears as a fine granular, free flowing sustained-release powder.

Dissolution Test

Formulation:

Creatine monohydrate	80%
Sucrose	10%
Calcium Carbonate	5%
Hydrogenated soy oil (Sterotex HM®)	5%

Time Release Pattern:

1 hour	46%
2 hrs	63%
4 hrs	78%
6 hrs	85%
10 hrs	100%

While the present invention is described above in connection with the preferred or illustrative embodiments, those embodiments are not intended to be exhaustive or limiting of the invention, but rather, the invention is intended to cover any alternatives, modifications or equivalents that may be included within its scope as defined by the appended claims.

What is claimed is:

1. A process for producing sustained-release particles comprising:
 - a) dispersing a core material in a mixer capable of mixing and heating said core material above 110°F, while adding a naturally derived animal or vegetable oil with a melting point above 110°F to the mixer until fully melted; b) mixing the molten oil with the core material until encapsulation; c) cooling said encapsulated material and discharging.
2. The process of claim 1 wherein the core material is selected from ; ace-inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatics; anti-cholesterolemics; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti- histamines; anti-hypertensive drugs; anti-infectives; anti-inflammatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor drugs; anti-tussives; anti- uricernic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; angiogenesis inhibitors; antacids; antiarthritics; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystokinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastro-intestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics; hypoglycernic agents; laxatives; migrain treatments; mineral supplements; mucolytics; narcotics; neuroleptics; neuromuscular drugs; NSAIDS; nutritional additives; peripheral vaso-dilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid

preparations; tranquilizers; uterine relaxants; vaginal preparations; vaso- constrictors; vago- dilators; vertigo agents; vitamins; wound healing agents, botanical substances, fungicides, and fertilizers.

3. The process of claim 1 wherein the animal or vegetable oil is a vegetable oil with a melting point between 120 degrees F and 200 degrees F.
4. The process of claim 1 wherein the animal or vegetable oil is a hydrogenated soy oil with a melting point of about 160 degrees F.
5. The process of claim 1 wherein the range of oil used is about 3% to 50% by weight in the finished particle.
6. The process of claim 1 wherein the range of oil is about 3% to 20% by weight in the finished particle.
7. The process of claim 1 wherein the range of oil is about 3% to 10% by weight in the finished particle.
8. The process of claim 1 wherein a high shear/high intensity mixer such as a Littleford mixer with a heating jacket is employed and the heat generated by the energy input is sufficient to melt the oil.
9. The process of claim 1 wherein a plow type mixer fitted with a heating jacket, tank, and heated lines to spray the oil is employed.
10. The process according to claim 1 further comprising a sugar or a mineral.
11. The process of claim 8 wherein the sugar is present in the melt from 1-30% by weight of finished particles.

12. The process of claim 8 wherein the sugar is present in the melt from 5-20% by weight of finished particles.
13. The process of claim 8 wherein the sugar is present in the melt at about 10% by weight of the finished particles.
14. The process of claim 8 wherein the sugar is selected from the following; sucrose, dextrose, lactose, polydextrose, maltodextrin, and maltose.
15. The process of claim 8 wherein the mineral is present in the melt from 1-20% by weight of the finished particles.
16. The process of claim 8 wherein the mineral is present in the melt from 5-10% by weight of the finished particle
17. The process of claim 8 wherein the mineral is present in the melt at about a 5% level and is calcium carbonate.
18. A solid sustained-release pharmaceutical composition comprising; a) a therapeutic agent, biological substance, fungicide or fertilizer as the core material, and b) an animal or vegetable oil with a melting point above 110 degrees F.
19. The composition according to claim 16 wherein the oil is present from 5-30% by weight in the finished particle.
20. The composition of claim 16 wherein the oil is present from 3-10% by weight in the finished particle.
21. The composition of claim 16 wherein the oil is present at a 5% level by weight in the finished particle.

22. The composition of claim 16 wherein the oil has a melting point of 110-200 degrees F.
23. The composition of claim 16 wherein the oil has a melting point of 120-180 degrees F.
24. The composition of claim 16 wherein the oil has a melting point of 160 degrees F.
25. The composition of claim 16 wherein the oil is a hydrogenated vegetable oil with a melting point above 110 degrees F.
26. The composition of claim 23 wherein the oil is hydrogenated soy oil with a melting point range of about 145-160 degrees F.
27. The composition of claim 16 wherein the core substance is selected from the following;
A drug, nutritional agent, botanical substance, biological substance, fungicide, or fertilizer.
28. The composition of claim 25 wherein the drug or nutritional agent is selected from ; ace-inhibitors; anti-anginal drugs; anti-arrhythmias; anti-asthmatics; anti-cholesterolemics; anti-convulsants; anti-depressants; anti-diarrhea preparations; anti- histamines; anti-hypertensive drugs; anti-infectives; anti-inflammatory agents; anti-lipid agents; anti-manics; anti-nauseants; anti-stroke agents; anti-thyroid preparations; anti-tumor drugs; anti-tussives; anti-uricemic drugs; anti-viral agents; acne drugs; alkaloids; amino acid preparations; anabolic drugs; analgesics; anesthetics; angiogenesis inhibitors; antacids; antiarthritics; antibiotics; anticoagulants; antiemetics; antiobesity drugs; antiparasitics; antipsychotics; antipyretics; antispasmodics; antithrombotic drugs; anxiolytic agents; appetite stimulants; appetite suppressants; beta blocking agents; bronchodilators; cardiovascular agents; cerebral dilators; chelating agents; cholecystokinin antagonists; chemotherapeutic agents; cognition activators; contraceptives; coronary dilators; cough suppressants; decongestants; deodorants; dermatological agents; diabetes agents; diuretics; emollients; enzymes; erythropoietic drugs; expectorants; fertility agents; fungicides; gastro-intestinal agents; growth regulators; hormone replacement agents; hyperglycemic agents; hypnotics; hypoglycemic agents; laxatives; migraine treatments; mineral supplements; mucolytics; narcotics; neuroleptics;

neuromuscular drugs; NSAIDS; nutritional additives; peripheral vaso-dilators; polypeptides; prostaglandins; psychotropics; renin inhibitors; respiratory stimulants; steroids; stimulants; sympatholytics; thyroid preparations; tranquilizers; uterine relaxants; vaginal preparations; vaso- constrictors; vago-dilators; vertigo agents; vitamins; wound healing agents.

27. The composition of claim 25 wherein the drug, nutritional , or botanical substance is selected from the following; niacin, L-arginine, creatine monohydrate, L-carnitine, aspirin, loratidine, lovastatin, vitamin C, garlic powder, polygonum cuspidatum root extract, astaxanthin, tocotrienol or co-enzyme Q-10.

SUSTAINED-RELEASE MICROENCAPSULATED DELIVERY SYSTEM

ABSTRACT

Disclosed is a process for producing sustained-release powders that is fast, efficient, and economical. The process involves melting an animal or vegetable oil with a melting point above 110 degrees F in specially designed mixer through either the work energy input of the mixer shaft itself, or a specially fitted plow type mixer equipped with a heating tank, cooling unit, jacket for hot water circulation, and heated lines with nozzles for atomizing the hot oil to be sprayed on. The entire manufacturing process can be completed in about 5-30 minutes, and results in small, sustained-release particles that are free flowing and solid at room temperature. The preferred oil is a hydrogenated soy oil with a melting point range of 145-160 degrees F. which is applied at about a 5% level by weight in a high shear mixer. Also included are sustained-release compositions for therapeutic agents such as drugs, botanicals, biological agents, fungicides, and fertilizers.

Declaration for Utility or Design Patent Application

As a below-named inventor, I hereby declare that my residence, post office address, and citizenship are as stated below next to my name and that I believe that I am the original, first, and sole inventor [if only one name is listed below] or an original, first, and joint inventor [if plural names are listed below] of the subject matter which is claimed and for which a patent is sought on the invention, the specification of which is attached hereto and which has the following title:

"Sustained-Release Microencapsulated Delivery System"

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration. I acknowledge a duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, Section 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Please send correspondence and make telephone calls to the First Inventor below.



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